



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> A01K 67/027, C07K 16/00, 16/24, 16/28 // C12N 15/85, 15/90	<b>A3</b>	<b>(11) International Publication Number:</b> WO 98/24893 <b>(43) International Publication Date:</b> 11 June 1998 (11.06.98)
<b>(21) International Application Number:</b> PCT/US97/23091 <b>(22) International Filing Date:</b> 3 December 1997 (03.12.97)  <b>(30) Priority Data:</b> 08/759,620 3 December 1996 (03.12.96) US  <b>(71) Applicant:</b> ABGENIX, INC. [US/US]; 7601 Dumbarton Circle, Fremont, CA 94555 (US).  <b>(72) Inventors:</b> JAKOBOVITS, Aya; 2021 Monterey Avenue, Menlo Park, CA 94025 (US). KUCHERLAPATI, Raju; 8 Gracie Lane, Darien, CT 06820 (US). KLAPHOLZ, Sue; 76 Peter Coutts Circle, Stanford, CA 94305 (US). MENDEZ, Michael; P.O. Box 787, El Granada, CA 94018 (US). GREEN, Larry; 70 Crestline Drive #2, San Francisco, CA 94131 (US).  <b>(74) Agents:</b> HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>  <b>(88) Date of publication of the international search report:</b> 20 August 1998 (20.08.98)  <div style="text-align: center; border: 1px solid black; width: 100px; margin: 20px auto;">29</div>
<b>(54) Title:</b> TRANSGENIC MAMMALS HAVING HUMAN IG LOCI INCLUDING PLURAL V <sub>H</sub> AND V <sub>K</sub> REGIONS AND ANTIBODIES PRODUCED THEREFROM  <b>(57) Abstract</b>  The present invention relates to transgenic non-human animals that are engineered to contain human immunoglobulin gene loci. In particular, animals in accordance with the invention possess human Ig loci that include plural variable (V <sub>H</sub> and V <sub>K</sub> ) gene regions. Advantageously, the inclusion of plural variable region genes enhances the specificity and diversity of human antibodies produced by the animal. Further, the inclusion of such regions enhances and reconstitutes B-cell development to the animals, such that the animals possess abundant mature B-cells secreting extremely high affinity antibodies.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23091

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A01K67/027 C07K16/00 C07K16/24 C07K16/28 //C12N15/85,  
C12N15/90

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A01K C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. JAKOBOVITS ET AL., : "Production of antigen-specific human antibodies from mice engineered with human heavy and light chain YACs" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 764, 1995, NEW YORK, NY, US, pages 525-535, XP002067728 see the whole document but specially pages 533-534  --- -/--	1-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 June 1998

Date of mailing of the international search report

25/06/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Mateo Rosell, A.M.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23091

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 94 25585 A (GENPHARM INT ) 10 November 1994  cited in the application  see page 1, line 19-33  see page 6, line 24 - page 7, line 23  see page 11, line 6 - page 12, line 19  see page 23, line 25 - page 24, line 7  see page 48, line 35 - page 49, line 22;  examples 1-5  see page 185, line 26 - page 190, line 31  see page 198, line 18-30  see page 202, line 16-36</p>	<p>1,2,  6-10,16,  24</p>
A	<p>WO 96 34096 A (CELL GENESYS INC) 31 October 1996  cited in the application  see page 2, line 20-34  see page 13, paragraph 31-33  see page 15, line 14-21; examples 2,3</p>	<p>1,16,17,  19-21,  23,24</p>
A	<p>WO 91 00906 A (GENETICS INST) 24 January 1991  see the whole document</p>	<p>1,11-16</p>
A	<p>L.D. TAYLOR ET AL.,: "A transgenic mouse that expresses a diversity of human sequence heavy and light chain immunoglobulins"  NUCLEIC ACIDS RESEARCH,  vol. 20, no. 23, 1992, OXFORD, GB,  pages 6287-6295, XP002041128  cited in the application  see the whole document</p>	<p>1-16,  26-28</p>
A	<p>M. BRUGGEMAN AND N.S. NEUBERGER:  "Strategies for expressing human antibody repertoires in transgenic mice"  IMMUNOLOGY TODAY,  vol. 17, no. 8, 1 August 1996, OXFORD, GB,  pages 391-397, XP002067729  cited in the application  see the whole document</p>	<p>1-28</p>
P,X	<p>M.J. MENDEZ: "Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice"  NATURE GENETICS,  vol. 15, no. 2, 1 February 1997, NEW YORK, NY, US,  pages 146-156, XP002067603  see the whole document</p>	<p>1-15</p>

-/--

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23091

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>A. JAKOBOVITS ET AL., : "Human immunity in mice engineered with megabase human heavy and kappa light chain YACs"</p> <p>THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY,</p> <p>vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US,</p> <p>page S113 XP002067604</p> <p>see abstract</p> <p style="text-align: center;">---</p>	1-15
P,X	<p>J.R.F. CORVALAN ET AL., : "Generation of fully human high affinity monoclonal antibodies to EGF receptor in mice"</p> <p>THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY,</p> <p>vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US,</p> <p>page s214 XP002067605</p> <p>see abstract</p> <p style="text-align: center;">---</p>	1,16,18, 20,22,24
P,X	<p>X.D. YANG ET AL.,: "Human monoclonal antibodies to human TNF-alpha generated from mice carrying human Ig loci"</p> <p>THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY,</p> <p>vol. 99, no. 1, part 2, 1 January 1997, SAINT LOUIS, MO, US,</p> <p>page s15 XP002067606</p> <p>see abstract</p> <p style="text-align: center;">-----</p>	1,16,19, 20,23,24

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna. Application No

PCT/US 97/23091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9425585 A	10-11-1994	US 5661016 A AU 3907895 A AU 6819494 A CA 2161351 A EP 0754225 A JP 8509612 T US 5625126 A JP 8140528 A	26-08-1997 29-02-1996 21-11-1994 10-11-1994 22-01-1997 15-10-1996 29-04-1997 04-06-1996
WO 9634096 A	31-10-1996	AU 2466895 A EP 0823941 A	18-11-1996 18-02-1998
WO 9100906 A	24-01-1991	NONE	